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## Citation

Li, Yin-Ge, and Xiang Gao. 2014. "Epidemiologic studies of particulate matter and lung cancer." Chinese Journal of Cancer 33 (8): 376-380. doi:10.5732/cjc.014.10063. <http://dx.doi.org/10.5732/cjc.014.10063>.

## Published Version

doi:10.5732/cjc.014.10063

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## Review

## Epidemiologic studies of particulate matter and lung cancer

Yin-Ge Li<sup>1</sup> and Xiang Gao<sup>1,2,3,4</sup>**Abstract**

Particulate matter (PM) plays an important role in air pollution, especially in China. European and American researchers conducted several cohort-based studies to examine the potential relationship between PM and lung cancer and found a positive association between PM and lung cancer mortality. In contrast, the results regarding PM and lung cancer risk remain inconsistent. Most of the previous studies had limitations such as misclassification of PM exposure and residual confounders, diminishing the impact of their findings. In addition, prospective studies on this topic are very limited in Chinese populations. This is an important problem because China has one of the highest concentrations of PM in the world and has had an increased mortality risk due to lung cancer. In this context, more prospective studies in Chinese populations are warranted to investigate the relationship between PM and lung cancer.

**Key words** Particulate matter, lung cancer, epidemiologic study

Particulate matter (PM), also known as particle pollution, is a complex mixture comprising components such as acids, organic chemicals, metals, and soil or dust particles<sup>[1]</sup>. Current environmental monitoring stations measure the concentration of inhalable particles that range in diameter from 2.5 to 10  $\mu\text{m}$  (referred to as  $\text{PM}_{10}$  in this review) and fine particles that have a diameter less than 2.5  $\mu\text{m}$  (referred to as  $\text{PM}_{2.5}$  in this review).

An estimated 5% of all deaths from lung cancer may be related to ambient air pollution<sup>[2]</sup>. In recent years, epidemiologists from around the world have developed several population-based cohorts to examine the potential relationship between lung cancer and particulate matter, especially  $\text{PM}_{10}$  and  $\text{PM}_{2.5}$ . Such cohorts include the Harvard Six Cities (HSC) study<sup>[3]</sup>, the American Cancer Society Cancer Prevention Study II cohorts (CPS-II)<sup>[4]</sup>, and the Netherlands

Cohort Study on Diet and Cancer<sup>[5]</sup>. We therefore reviewed current research on the association of particle pollution with risk and mortality of lung cancer.

## PM and Lung Cancer Mortality

### Fine particles ( $\text{PM}_{2.5}$ )

The positive relationship between  $\text{PM}_{2.5}$  concentrations and increased lung cancer mortality has been investigated in two large, US-based cohort studies, the HSC<sup>[3]</sup> and the CPS-II<sup>[4]</sup>, and several other prospective cohorts as reviewed below.

In the HSC study, a modest association was found between higher concentration of  $\text{PM}_{2.5}$  and increased lung cancer mortality. In this cohort, approximately 8,000 participants aged 25 to 74 years were randomly sampled between 1975 and 1976 from six US cities.  $\text{PM}_{2.5}$  data were collected from monitoring stations that were located in the center of each community. The International Classification of Disease, 9th Revision (ICD-9), was used to certificate lung cancer carriers. At baseline, approximately 35% of the participants were current smokers with an average smoking history of over 20 years, and the percentage of smokers remained somewhat consistent during follow-up. During the past 20 years, three reports have been published based on this cohort<sup>[3,6,7]</sup>. In the first report, which was based on follow-up results up to 1991, the adjusted lung cancer

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**doi:** 10.5732/cjc.014.10063

mortality rate ratio (RR) was 1.37 [95% confidence interval (CI): 0.81–2.31] for each 10  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$  concentration after adjustment for age, sex, body mass index (BMI), education, and smoking status<sup>[3]</sup>. In the second report, which was based on follow-up results through 1997, the relevant lung cancer mortality RR decreased slightly to 1.27 (95% CI: 0.96–1.69) for a 10  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$  concentration<sup>[6]</sup>. Of note, the annual concentration of  $\text{PM}_{2.5}$  also decreased slightly when compared to the first report (from 1974 to 1989). In the third report on  $\text{PM}_{2.5}$  and lung cancer, for which 2009 was used as the follow-up end point, the adjusted cancer mortality RR was 1.37 (95% CI: 1.07–1.75) for a 10  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$  concentration<sup>[7]</sup>.

In CPS-II, 1.2 million adults aged 30 years or older from all 50 states have been enrolled in the cohort since 1982<sup>[4]</sup>. In the analysis of PM and lung cancer mortality, 794,784 participants were included. Lung cancer mortality from 1982 to 1998 was assessed based on the ICD-9 code. Air pollution exposure information was collected from the Environmental Protection Agency Aerometric Information Retrieval System (AIRS) and Inhalable Particle Monitoring Network (IPMN). The adjusted lung cancer mortality RR was 1.14 (95% CI: 1.04–1.23) for a 10  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$  concentration<sup>[4,8]</sup>. In another study that was based on the CPS-II cohort but focused on never-smokers, the lung cancer mortality RR was 1.19 (95% CI: 0.97–1.47) for a 10  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$  concentration, which was higher than the lung cancer mortality RR for the general population<sup>[9]</sup>.

A similar positive association between  $\text{PM}_{2.5}$  and lung cancer mortality was also found in a Japanese cohort<sup>[10]</sup> and an Italian cohort<sup>[11]</sup>. In the Japanese cohort study, the adjusted lung cancer mortality hazard ratio (HR) was 1.24 (95% CI: 1.12–1.37) for a 10  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$  concentration<sup>[10]</sup>. This Japanese study comprised 63,530 participants from three cities (Miyagi, Aichi, and Osaka), and follow-up continued from 1974 to 1983. Data collected from monitoring stations operated by the Ministry of Environment in Japan showed that the 10-year average  $\text{PM}_{2.5}$  concentration ranged from 24.0  $\mu\text{g}/\text{m}^3$  to 59.9  $\mu\text{g}/\text{m}^3$ . In the Italian study, approximately 1.3 million participants aged 30 years or older were followed up for nine years. Using a chemical transport model<sup>[12]</sup> to measure  $\text{PM}_{2.5}$  concentration around the participants' residential areas, a 5% higher lung cancer mortality risk was observed for a 10  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$  concentration (95% CI: 1.01–1.10)<sup>[11]</sup>.

### Inhalable particles ( $\text{PM}_{10}$ )

The UK-based National English Cohort<sup>[13]</sup> and a German cohort<sup>[14]</sup> for women explored the association between  $\text{PM}_{10}$  and lung cancer mortality.

In the National English Cohort, which included 835,607 participants aged 40 to 89 years who were followed up from 2003 to 2007, both  $\text{PM}_{10}$  and  $\text{PM}_{2.5}$  showed a positive association with lung cancer mortality, with an adjusted HR of 1.08 (95% CI: 1.03–1.14) for  $\text{PM}_{2.5}$  and 1.07 (95% CI: 1.02–1.13) for  $\text{PM}_{10}$ . At the sites studied, the annual concentration of  $\text{PM}_{10}$  ranged from 12.6  $\mu\text{g}/\text{m}^3$  to 29.8  $\mu\text{g}/\text{m}^3$ ,

with a mean concentration of 19.7  $\mu\text{g}/\text{m}^3$ ; and  $\text{PM}_{2.5}$  concentration ranged from 8.5  $\mu\text{g}/\text{m}^3$  to 20.2  $\mu\text{g}/\text{m}^3$ , with a mean concentration of 12.9  $\mu\text{g}/\text{m}^3$ <sup>[13]</sup>.

In the German cohort, approximately 4,800 women aged mid-50s were followed up from two cross-sectional studies, one established in the 1980s and the other in the 1990s, followed until 2008. Two methods were used when assessing air pollution exposure: geographic information system (GIS)-calculated distances between residential addresses and the nearest major road, and information from air-monitoring stations close to residential addresses. In this study, each 7  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{10}$  concentration was associated with a 84% increased risk of lung cancer mortality (adjusted RR: 1.84; 95% CI: 1.23–2.74)<sup>[14]</sup>.

## PM and Lung Cancer Risk

To date, only three prospective studies have been published to examine the relationship between PM and lung cancer risk, generating inconsistent results. However, among never-smokers, two of the three studies showed a significant association between lung cancer risk and  $\text{PM}_{2.5}$ .

In 2006, results of a Europe-based, nested case-control study, contained within the European Prospective Investigation into Cancer and Nutrition cohort<sup>[15]</sup>, showed that air pollution was not significantly associated with lung cancer risk<sup>[16]</sup>. Lung cancer certificates were based on cancer registries and hospital discharge data. Air pollution exposure data was collected from monitoring station networks and adjusted the distance between the participants' home address and main roads, using the traffic loads to determine the roads' categories. In the nested case-control study, the control group ( $n = 312$ ) included participants from locations where the  $\text{PM}_{10}$  concentration was lower than 27  $\mu\text{g}/\text{m}^3$ , whereas the case group ( $n = 113$ ) included participants from locations where the  $\text{PM}_{10}$  concentration was higher than 27  $\mu\text{g}/\text{m}^3$ . In the case group, no significant relationship was found between higher  $\text{PM}_{10}$  concentration and increased risk of lung cancer [odds ratio (OR) = 0.91; 95% CI: 0.70–1.18]. However, a small sample size (113 cases and 312 controls) limited the power of this finding.

Similar non-significant results were found in another Europe-based study<sup>[5]</sup>. After 11 years of follow-up (1986–1997), results from this prospective study, based on the Netherlands Cohort Study on Diet and Cancer ( $n = 111,816$ ), showed that  $\text{PM}_{2.5}$  concentrations were not associated with lung cancer risk (RR: 0.81; 95% CI: 0.63–1.04). However, in a subgroup analysis based on 40,114 non-smokers, a significant positive association between higher  $\text{PM}_{2.5}$  concentrations and increased lung cancer risk was observed (RR: 1.47; 95% CI: 1.01–2.16). In this study, cancer certificates utilized the ICD for Oncology code. Air pollution data were collected from the National Air Quality Monitoring Network, and the distance between residential addresses and major roads were adjusted by using GIS. Baseline characteristics for participants and residential traffic information were collected simultaneously in 1986. During follow-up,

PM<sub>2.5</sub> exposure ranged from 22.9 µg/m<sup>3</sup> to 36.8 µg/m<sup>3</sup>, with a mean concentration of 28.2 µg/m<sup>3</sup>.

In contrast, a significant association was observed between lung cancer risk and PM in a prospective study based on the European Study of Cohorts for Air Pollution Effects. This prospective study used data from 17 cohorts in nine European countries that included 312,944 participants with an average follow-up of 12.8 years<sup>[17]</sup>. Light reflectance was used to measure PM concentration in each cohort location during different seasons, and land-use regression models were used as predictors for each pollutant. Information about participant addresses and area traffic was also included in the analysis. A meta-analysis to examine the relationship between PM and lung cancer risk revealed an adjusted HR of 1.22 (95% CI: 1.03–1.45) per 10 µg/m<sup>3</sup> increase in PM<sub>10</sub> concentration and 1.18 (95% CI: 0.96–1.46) per 5 µg/m<sup>3</sup> increase in PM<sub>2.5</sub> concentration. In addition, this Europe-based, 17-cohort study showed a higher lung cancer risk related to PM in non-smokers (HR: 1.39, 95% CI: 0.94–2.06 for PM<sub>10</sub>; HR: 1.21, 95% CI: 0.61–2.40 for PM<sub>2.5</sub>)<sup>[17]</sup>.

## Limitations of Previous Epidemiologic Studies

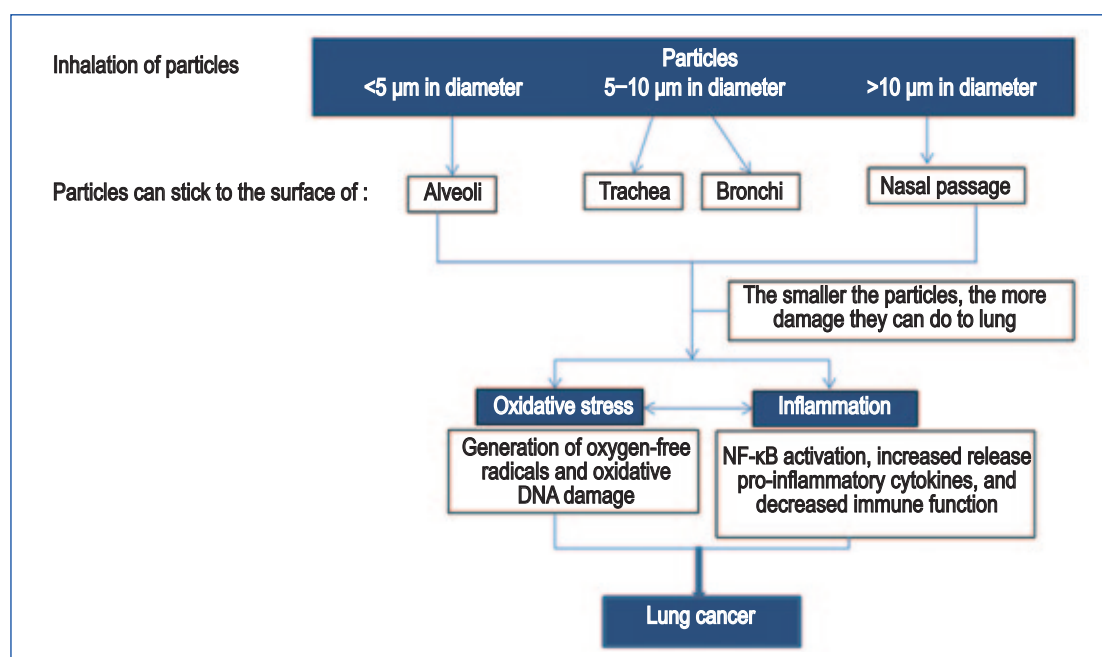
As reviewed above, previous epidemiologic studies have reported a consistent relationship between high particle pollution with lung cancer mortality. Yet, results have been mixed regarding lung cancer risk, partly because of the limited number of studies conducted on this topic. However, some limitations should be considered for data interpretation.

First, in the previous studies, air pollution information was

based on monitoring station data that included both the target communities and surrounding areas, but was not based on individual houses. As a result of the inaccuracy on PM data collection, misclassification of exposure was inevitable, which may have attenuated the potential relationship between PM concentration and lung cancer risk<sup>[3-10,13,14,16]</sup>. Residual confounding is another concern. Most of the studies did not consider several important covariates, such as information on outdoor air pollution infiltration into the home (i.e., air exchange rate), workplace locations, indoor air quality, and time spent in traffic and indoors<sup>[5,10]</sup>. These factors are purportedly associated with both exposure and lung cancer. Another source of residual confounding is that only baseline covariates were adjusted in the models. In long-term follow-up, participant baseline characteristics could change (such as changes in residence, neighborhood environment, lifestyle, and socioeconomic status) over time and influence individual risk factors (such as changes in alcohol consumption, smoking, diet, and BMI), affecting the collection of mortality information.

## Potential Mechanisms Underlying the Relationship Between PM Concentration and Lung Cancer Risk

There are several potential mechanisms through which PM may influence lung health (**Figure 1**). These include cytotoxicity induced through oxidative stress, generation of oxygen-free radicals, mutagenicity or oxidative DNA damage, and stimulation of pro-inflammatory factors<sup>[18]</sup>.



**Figure 1.** Overview of how particulate matter impacts the lungs and may lead to lung cancer. NF-κB, nuclear factor kappaB.

## PM and Lung Cancer in China

Over the past decades, economic development in China has progressed dramatically. However, during this development, the ambient air quality has decreased exponentially. Even though the Chinese government has made an effort to control air pollution and improve air quality, the ambient air pollution level is still among the highest in the world<sup>[19]</sup>. In addition, among Chinese males, the smoking population is sizable and contributes to large amounts of second-hand smoke<sup>[20]</sup>. Lung cancer mortality was associated with both smoking and PM in European and American studies. In China, lung cancer mortality has also increased in past decades<sup>[21]</sup>, but to our knowledge, only one prospective study in China focused on the relationship between ambient air pollution and lung cancer mortality. In this study, adjusted mortality risk for lung cancer increased by 3.4% (95% CI: 0.997–1.07) for each 10  $\mu\text{g}/\text{m}^3$  increase in  $\text{PM}_{2.5}$  concentration<sup>[19]</sup>; however, the population studied did not include a representative sample of Chinese. Because most studies in China

focused on indoor air pollution and health quality<sup>[22]</sup>, large population-based and long-term exposure prospective cohorts are needed to better understand the relationship between outdoor particle pollution and lung cancer.

In conclusion, several prospective studies consistently showed a relationship between particle pollution and lung cancer mortality. This observation is of particular significance for China due to its high air pollution levels. However, further investigations are essential to explore the association between PM and lung cancer risk. Future studies should also consider in more detailed individual confounders such as changes in age, residence, neighborhood, lifestyle, and socioeconomic status. Furthermore, different methods should be introduced when collecting cancer and air pollution exposure information.

Received: 2014-04-28; revised: 2014-07-11;  
accepted: 2014-07-29.

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